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Comparison of sella tursica volumes among patients with primary empty sella, sheehan syndrome and healthy individuals

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Abstract

Background: Sella turcica volumes vary greatly among patients both with and without pituitary dysfunction. We aim to investigate differences in sella turcica volumes and pituitary hormone levels among patients with primary empty sella (PES), sheehan syndrome (SS) and healthy individuals.

Material and methods: We performed a retrospective case-control study of both the sella turcica volume and pituitary hormone levels of 75 female patients. These patients were divided into three groups: those with PES group, SS group and those with no known pituitary dysfunction.

Results: We demonstrated that sella turcica volumes were measured as 895.6±330.6 mm3, 125.8±50.8 mm3 and 679.5±129.5 mm3 in PES group, SS group and healthy groups respectively. There was statisticaly difference between PES group and healthy group. Additionaly, SS group had statisticaly lower sella turcica volume than healthy group. PES group had statisticaly lower adrenocorticotropic hormone, cortisol, free T4, prolactin and insulin like growth factor-1 levels than healthy group. All of the SS group had panhypopituitarism.

Conclusion: Enlarged sella turcica volume may be a risk factor for primary empty sella syndrome and primary empty sella related low hormone levels. Furthermore, we also demonstrate that smaller sella turcica volume may be a risk factor for developing Sheehan Syndrome. As such, we propose that sella volume may therefore be used as a predictor for devoloping pituitary hormone deficiencies in the future. Further clinical studies are required to better understand the relationship between sella turcica volume and pituitary hormone levels.

Key words: sheehan syndrome, primary empty sella, sella tursica volume

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Introduction

The sella turcica is a saddle-shaped depression in the body of the sphenoid bone of the human skull [1]. The sella turcica is known to vary greatly in volume among individuals. Physiological conditions (e.g: puberty, pregnancy) and non-physiological conditions (e.g: neuroendocrine disorders) can change the size of the sella turcica as well as the amount of unoccupied sellar space. However, measurements of the sella alone in clinical situations are generally regarded as unreliable indicators of disease [2].

Empty sella syndrome is defined as the herniation of the subarachnoid space, with displacement of the pituitary toward the posteroinferior wall, often associated with some degree of flattening of the pituitary gland. In the absence of surgery, radiation therapy, or medical intervention for an intrasellar tumor, this entity has been termed as primary empty sella (PES) [3]. With increased use of computed tomography (CT) and magnetic resonance imaging (MRI) techniques, PES has become a frequent incidental finding. Sheehan Syndrome (SS) occurs due to excessive bleeding during or after child birth leading to hypovolemia, a rapid drop in peripheral blood pressure, and subsequent necrosis of the pituitary gland [4]. Scarring of the pituitary gland later takes place, and the resulting syndrome is associated with a decrease

in gland size and hormone deficiencies. Sella turcica volumes of patients with SS are significantly lower than that of healthy women [5].

In our study, we aim to investigate differences in sella turcica volumes and pituitary hormone levels among patients with PES, SS and healthy individuals.

Material and methods

Study design and participants

A retrospective cross-sectional study was performed which included 75 female participants between 18-65 years of age who were seen at the Kayseri Education and Research Hospital Endocrinology and Metabolic Diseases Clinic between 2013 and 2016. The participants were divided into three separate groups as follows: 41 women with PES, 21 women with SS, and 13 healthy women on whom MRI had been performed, showing normal pituitary anatomy. Each of the patients with SS had panhypopituitarism, or low levels of all pituitary hormones, and took levothyroxine and prednisolone replacement therapy, and were therefore excluded from hormone comparison with the patients with PES and healthy patients. Patients were also excluded from the study in cases of pregnancy, breastfeeding, exogenous estrogen use, hypothalamic and pituitary tumors, primary hypothyroidism, Addison's disease, polycystic ovary syndrome, psychosis, depression, cranial irradiation, history of intracranial space-occupying lesions, or previous intracranial surgery, history of any cranial trauma, all of which can secondarily alter hormone levels.

This study was performed in accordance with the Helsinki Declaration and approved by the local ethics committee. This article does not contain any studies with human participants or animals performed by any of the authors. Based on radiographic reports retrospectively reviewed article was not given any identification data. So patients have not been taken in the consent form.

Laboratuary evaluation

Blood samples for all hormonal assays and stimulation tests were drawn from patients in the morning at 8.00 am. Routine biochemical examinations, complete blood counts, thyroid function tests and basal pituitary hormone levels (serum growth hormone (GH), Insulin like growth factor-1 (IGF-1), follicle stimulating hormone (FSH), luteinising hormone (LH), prolactin, adrenocorticotropic hormone (ACTH), cortisol, thyroid stimulating hormone (TSH) and estradiol) were recorded for each patient. Insulin tolerance test (ITT) was performed after an overnight fast, and blood samples were obtained prior to the intravenous administration of 0.1 U/kg (0.2 U/kg if BMI>30 kg/m2) soluble regular insulin, as well as immediately afterward hypoglycemia (minute-0), and after 30, 60, 90 and 120 min. All patients had biochemically confirmed hypoglycemia (<40 mg/dL). Peak cortisol level>18µg/dl were accepted as having an adequate response to ITT [6,7].

MRI protocol

Today MRI is the most exclusive and the most common imaging technique for the evaluation pathology of cellar and paracellar space [8]. All MRI scans were performed with a 1.5 Tesla Philips Intera MR scanner. (Philips Medical Systems; Amsterdam; The Netherlands). Pituitary MRI protocol; sagittal and coronal T1-weighted; Coronal T2-weighted sequences and contrast dynamic T1 taken following injection consisted mainly and late phase coronal and sagittal T1-weighted images. Sella turcica volumes (mm3) were measured by using the DiChiro formula (0.5 X (length X width X depth)) [9]. One experienced neuroradiologists evaluated the images.

Statistical analysis

All statistical analyses were performed with the SPSS 15.0 Software. Descriptive data are presented as mean ± Standart deviation, percentages, and occasionally as a range of minimum–maximum. Distribution of data was tested by the Kolmogorov–Smirnov test before comparison and correlation tests. The independent samples t-test was used for normally distributed data. The Spearman's test was used for correlation analysis, because data were not normally distributed. In addition, the X2 test was used to evaluate a relationship between partial hormone deficiency and partially empty sella. P values less than 0.05 (P<0.05) was considered statistically significant.

Results

The mean ages of the PESG, SSG, and HG were 46.5±13.1 years, 44.9±11.5 years, and 45.5±12.4 years respectively. There was no statitical difference among groups in regards to age (p=0.70).

Mean sella volumes were measured as: 895.6±330.6 mm3 in the PES group (PESG), 125.8±50.8 mm3 in the SS group (SSG), and 679.5±129.5 mm3 in the healthy group (HG). When the PESG and SSG were compared with the HG with regard to sella volumes, the PESG had statistically larger sella turcica

Figure 1

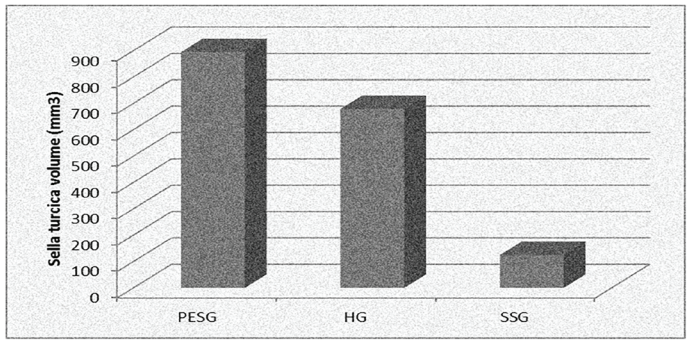

Table 1 Introductory Statistics on Variables

	PESG n = 41	HG n = 13	P
ACTH (0–46 pg/ml)	20.6±9.9	29.8±1.5	0.02
Kortizol (6.2–19 µg/dl)	10.0±3.4	13.1±5.3	0.02
Prolactin (3.3–26.7 ng/ml)	9.9±5.9	19.4±2.8	0.04
IGF-1 (55–212 ng/ml)	107.6±45.8	144.4±46.4	0.04
TSH (0.4–5.6 mIU/ml)	2.2±1.5	1.3±0.6	0.70
T4 (0.54–1.24 ng/dl)	0.8±0.1	1.5±0.9	0.01
FSH (premenopause folliculary phase) (3.85-8.78 mIU/ml)	13.4±4.3	15.4±6.9	0.29
FSH (postmenopause) (16.74-113.6 mIU/ml)	48.3±7.6	39.4±13.9	0.31
LH (premenopause folliculary phase) (2.12-10.89 mIU/ml)	8.8±1.9	9.0±3.4	0.87
LH (postmenopause) (10.8-58.6 mIU/ml)	21.8±4.0	11.2±4.6	0.79
Estradiol (premenopause folliculary phase) (27-122 pg/ml)	88.5±13.6	69.5±16.5	0.72
Estradiol (postmenopause) (20-40 pg/ml)	11.8±6.9	10.2±3.2	0.60

PESG: Primary empty sella group, HG: Healthy group, SSG: Sheehan Syndrome group, ACTH: adrenocorticotropic hormone, IGF-1: Insulin like growth factor-1, TSH: thyroid stimulating hormone, FSH: follicle stimulating hormone, LH: luteinising hormone

volumes than the HG (p=0.03), and the SSG had statistically lower sella turcica volumes than the HG (p<0.001) (Figure 1).

The PESG and the HG were also compared in regards to ACTH, cortisol, TSH, FT4, prolactin, and IGF-1 levels. Although patients in both the PESG and the HG had levels of ACTH, cortisol, FT4, prolactin, and IGF-1 within the normal limits, patients in the PESG had statisticaly significantly lower hormone levels than those of the HG (p=0.02); there was not a statistically significant difference in TSH, FSH, and LH levels between said groups (p=0.16). There was however a negative correlation between sella volumes and TSH levels (p=0.006, r=-37). Other hormone levels were not correlated with sella volumes (p=0.24) (Table 1). IGF-1 levels were evaluated according to age-appropriate normative ranges. For this reason, any dynamic test was performed due to GH deficiency.

Because of low cortisol levels in the PESG (<5 μg/dl), 3 patients were administered an insulin tolerance test, After ITT, plasma cortisol peak levels were detected at >18μg/dl and were accepted as adequate cortisol response.

Discussion

Sella volume is a parameter that can give clues about pituitary disorders. In this study, sella volumes were compared among PESG, SSG, and HG. Whereas SS group has the lowest sella volume among these groups, PESG had higher sella volume than HG.

The most common pathological conditions that increase sella turcica volume are intrasellar adenomas and empty sella syndrome [10,11]. Other more rare conditions may also cause enlargement, such as Rathke's cleft cysts and aneurysms [12]. An abnormally small sella is less likely to occur, and is seen in primary hypopituitarism, growth hormone deficiency, Williams syndrome, and Sheehan syndrome [13,14]. In this study, PESG patients had been known any reason related with enlargement sella volumes.

The term empty sella was first used by Sheehan and Summer in 1949 [15]. PES has been reported in 6–20% of unselected autopsies and female/male ratio of 4/1 [16].
PES may be a radiological finding in asymptomatic patients or it may be associated with variable clinical conditions such as neurological, visual, and/or endocrine disorders [17]. Classically, pituitary function is normal in patients with PES [18]. However, pituitary dysfunction can be explained by the chronic compression of the pituitary gland and the pituitary stalk by cerebrospinal fluid [19]. The most common pituitary disorders associated with PES are hyperprolactinemia and GH deficiency.

Different degrees of hypopituitarism ranging from 8 to 60 % have been reported [20,21]. According to Ghatnattiet al. 50% of empty sella were associated with endocrine dysfunction, the most common being hyperprolactinemia in 20.8%, isolated GH deficiency in 12.5%, isolated central hypothyroidism in 4.1%, isolated hypocortisolemia in 4.1%, and multiple pituitary hormone deficiencies in 4.1% [22]. When PESG compared with HG, PESG's ACTH, cortisol, FT4, prolactin and IGF-1 levels although the normal range, was statistically significant lower (p<0.05). Between FSH, LH and TSH values, there was no statistically significant difference. Sella volume may be used a predictor for devoloping hormone deficiency in future.

Sheehan Syndrome was first described by Sheehan in 1937 and has an incidence of 1 in 10.000. The exact pathophysiology of SS is not clearly understood. However, the end result is pituitary infarction secondary to arrest of blood flow to the anterior lobe of the pituitary gland, which may be due to vasospasm, thrombosis or vascular compression [23]. A relatively smaller sella turcica volume has been suggested to play an important role in the etiopathogenesis of SS [24]. The study of Diri et al. examined 114 patients with SS, all of whom had GH and gonadotropin deficiencies, while 90.4% of patients had concominant TSH deficiency, 71.9% had concominant ACTH deficiency, and 71.1% had concominant prolactin deficiency at the time of diagnosis. Partial hypopituitarism due to SS has also been reported in other studies [25,26]. In this presented study all of the patients with SS had panhypopituitarism and they have taken prednisolon and levotiroksin hormone replacement therapy. So the hormonal comparison wasn't couldn't made between SSG, PESG and HG.

The normal range of adult sella turcica size is reportedly between 240 and 1092 mm3 [9]. In the study of Sherif et al. high resolution CT was used to assess the size and contents of the pituitary fossa in 57 women with SS and 17 healthy female control subjects; the recorded sella turcica volumes showed wide variation. The mean sella turcica volume for all patients was 565±292 mm3 in contrast to a mean volume for the controls of 922±155mm3, which was statistically significant (p<0.001) [24]. Diri et al. measured the sella turcica volumes in two groups; the first group included 67 women with SS, and the second group included 29 healthy females. The mean sella turcica volume of SS patients was calculated as 340.5±214 mm3 (range, 40–1008), which was significantly lower than the healthy group sella turcica volumes with 602.5 ± 192 mm3 (range, 308–1040) (P<0.001). The minimum sella turcica size in healthy women was found to be 308 mm3, which the SS group was well under [27]. In this study, sella turcica volumes were measured as 895.6±330.6 mm3, 125.8±50.8 mm3 and 679.5±129.5mm3 in the PESG, SSG, and HG respectively. Sella turcica volumes of patients with PESG compared with HG revealed statistically significant increase (p<0.05). Sella turcica volumes of patients with SSG compared with HG revealed statistically significant decreased (p<0.001).

There were some limitations in this study. Firstly this was a retrospective, whereas in a prospective study, sella volume-related pituitary functions could be understood more clearly. Secondly was low number of participants; for this reason we cannot make generalizations.

In conclusion, presented study results demonstrate that sella turcica volumes were increased in patients in the PESG when compared with those of the HG, and that sella turcica volumes were decreased in patients with SSG when compared with those of the HG. Both patients with PESG and those of the HG displayed pituitary hormone levels within the normal limits. However, patients with PESG had pituitary hormonal levels significantly closer to the lower limit of normal than HG. The larged sella turcica volume we observed in patients with PES suggest that it may be a risk factor for devoloping PES. The decreased sella turcica volume of SS suggests that it may be associated with low hormone levels seen in SS. Furthermore, we also propose that even if the hormone levels in patients with PES are within normal limits, we believe they may benefit from close monitoring, as the hormone levels we observed were of the lower limit of normal, and were much lower than levels of healthy individuals.

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